Refer to: Hepner GW, Piken E, Lechago J: Abnormal aminopyrine metabolism in patients with chronic hepatitis. West J Med 134:390-393, May 1981

Abnormal Aminopyrine Metabolism in Patients With Chronic Hepatitis

GERSHON W. HEPNER, MD; EDWARD PIKEN, MD, *and*
JUAN LECHAGO, MD, PhD, *Torrance, California*

Aminopyrine metabolism was studied by the aminopyrine breath test in 21 control subjects, 24 patients with untreated chronic active hepatitis (CAH), 4 patients with treated CAH and 17 patients with chronic persistent hepatitis (CPH). Aminopyrine breath tests gave abnormal results in 20 of 24 patients with untreated CAH. Findings were normal in all patients with treated CAH or with CPH. This test may be helpful in discriminating between CAH and other forms of chronic hepatitis.

CHRONIC ACTIVE HEPATITIS has a wide spectrum of clinical and histological severity.[1] In many patients, the course is progressive but may be affected by drugs such as prednisone or azathioprine.[2-5] In others, the disease may progress slowly, if at all. In contrast, persistent hepatitis nearly always has a benign prognosis and requires no therapy.[6] We have previously reported that hepatic N-demethylation of aminopyrine labeled with carbon 14, determined by the aminopyrine breath test (ABT), is impaired in most patients with cirrhosis[7,8] or hepatic neoplasm,[8,9] and this has been confirmed by other investigators.[10-12] We therefore carried out a study to determine whether it could be of any assistance in discriminating between patients with different forms of chronic hepatitis. Our data suggest that results of an ABT are always normal in patients with chronic persistent hepatitis (CPH) and nearly always abnormal in patients with untreated chronic active hepatitis (CAH).

From the Division of Gastroenterology and the Department of Pathology, Harbor-UCLA Medical Center, Torrance, California.
Submitted, revised, November 24, 1980.
Reprint requests to: Gershon W. Hepner, MD, 2080 Century Park East, Suite 903, Los Angeles CA 90067.

Patients and Methods

Patients

The patients in the study included 21 control subjects without liver disease, 24 patients with chronic active hepatitis and 17 patients with chronic persistent hepatitis. In all patients in the last two groups the diagnoses were made by liver biopsy carried out within two weeks of the aminopyrine breath test. The control subjects included 11 men and 10 women, median age 44, and none of them had any history of liver disease or had taken any drugs, including alcohol, for at least two weeks before the study. Of the controls, six had rheumatoid arthritis, eight had peptic ulcer disease, four had hypertension and three had reflux esophagitis. The patients with CAH included 14 who were positive for hepatitis B surface antigen (HBsAg), all with a previous history of

ABBREVIATIONS USED IN TEXT

ABT = aminopyrine breath test
CAH = chronic active hepatitis
CPH = chronic persistent hepatitis
HBsAg = hepatitis B surface antigen

intravenous drug abuse, plus two other HBsAg-negative subjects who had also had a previous history of drug abuse. The patients with CPH included eight who were HBsAg-positive, all of whom had a history of intravenous drug abuse. As far as could be determined, none of the patients with liver disease had taken any drugs, including alcohol, methadone or barbiturates, for at least two weeks before the aminopyrine breath test.

Second aminopyrine breath tests were done on a number of subjects. In four control subjects with rheumatoid arthritis studies were done twice, once before starting therapy with prednisone, 20 mg per day, and again after one month of this therapy. Studies were done twice in four patients with CAH, once before starting prednisone therapy and again, 6 to 12 months later, while they were taking prednisone but were in apparent remission from their CAH. These four patients all were found to have cirrhosis in pretreatment liver biopsy studies; posttreatment liver biopsy studies showed remission of the disease. To assess the reproducibility of the ABT, tests were done twice in six patients with untreated CAH at intervals of one week.

The clinical and biochemical features of the patients with CAH and CPH at the time of the study are illustrated in Table 1. The two groups differed significantly in only two features, serum bilirubin and gamma globulin values, both of which were higher in the patients with CAH than in those with CPH. Of 21 patients with CAH, 9 had serum bilirubin values greater than 2.0 mg per dl in contrast to only 3 of 17 patients with CPH. Gamma globulin values were greater than 1.5 grams per dl in 6 of 10 patients with CAH and in none of the 11 patients with CPH in whom this was determined. We excluded from the studies patients with ascites or encephalopathy because we felt that in such patients no special studies such as an aminopyrine breath test are necessary to determine whether or not the patient has chronic active liver disease.

TABLE 1.—*Initial Features in Chronic Active Liver Disease*

	CAH	CPH
Clinical features		
Sex, male	15	12
Age, year (median)	40	36
Time since diagnosis, months (median)	16	13
Biochemical features		
Albumin, grams/dl (median)	3.4	3.8
Bilirubin, mg/dl (median)	2.3	0.9*
Serum aspartate aminotransferase (SGOT), IU/liter (median)	164.0	178.0
Prothrombin time, percent normal (median)	92.0	100.0
Gamma globulin, grams/dl (median†)	2.2	1.4*

CAH = chronic active hepatitis
CPH = chronic persistent hepatitis

*$P < 0.01$.
†Determined in 10 patients with CAH and in 11 patients with CPH.

Histological Studies

Liver biopsy specimens were stained by conventional techniques and examined by one of us (J.L.) without reference to the clinical or biochemical status of the patient or the aminopyrine breath test. The criteria for diagnosing CAH included chronic inflammation in portal areas, significant piecemeal necrosis, regeneration of hepatocytes and, occasionally, bridging necrosis. In addition, 10 of 24 patients with CAH had extensive nodular regeneration and fibrosis, such that cirrhosis was the dominating feature. CPH, on the other hand, was characterized by absence of parenchymatous damage and presence of moderate portal inflammation without piecemeal necrosis.

Aminopyrine Breath Test

Aminopyrine breath tests were carried out as previously described.[7] Briefly, this test involves oral administration of a trace dose (1 to 2 μCi) of aminopyrine labeled with carbon 14 (Amersham, Chicago, Illinois), followed after two hours by collection of a single sample of breath, 2 mmole of carbon dioxide, in duplicate vials containing 2 mmole ethanolic hyamine with thymolphthalein as indicator. The specific activity of breath carbon dioxide tagged with carbon 14 ($^{14}CO_2$) is determined by counting the ethanolic hyamine in a liquid scintillation counter after addition of a liquid scintillation cocktail. Output of breath $^{14}CO_2$ in two hours is determined by multiplying mean $^{14}CO_2$ specific activity by the endogenous output of carbon dioxide (mmoles per kg of body weight per hour).[14] The data are

then expressed as the percentage of administered carbon 14 excreted in breath $^{14}CO_2$ in two hours (ABT). In previous studies, we have shown that the ABT correlates with the metabolic clearance rate of aminopyrine in control subjects[7,15] and in patients with hepatocellular disease,[7,14] hepatic neoplasm,[8,9] cholestasis[16] or congestive cardiac failure.[17] To minimize variability of data due to variability of endogenous carbon dioxide output,[18,19] all subjects were studied while nonambulant and fasting.

Serum Biochemistry

Determinations of serum albumin, bilirubin, aspartate aminotransferase (SGOT) and alanine aminotransferase (SGPT) were carried out by an automated method using the Vickers M-300. Gamma globulin values were found by cellulose acetate electrophoresis. Prothrombin time was determined using an automatic method using the Electra 600.

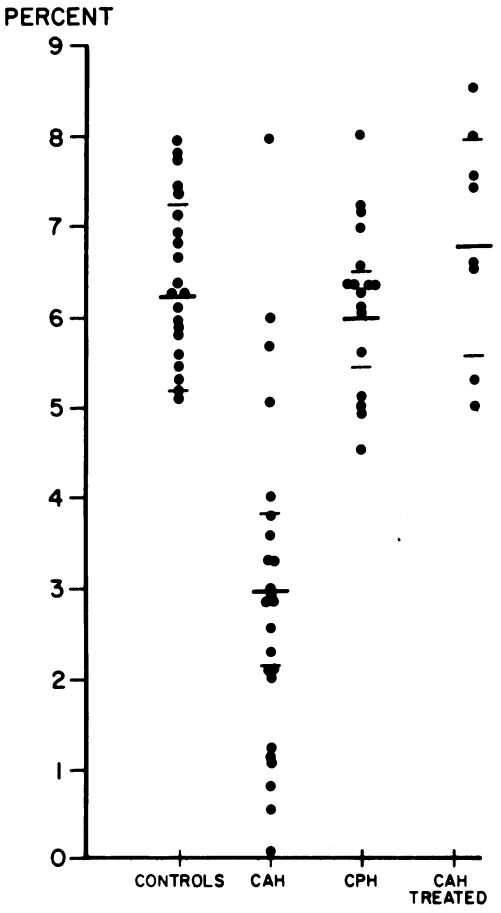

Figure 1.—Results of aminopyrine breath tests in the patients studied.

Statistics

Comparisons between controls and patients with liver disease were made by analysis of variance. Comparisons between patient groups were made using Student's t test. Where appropriate, a paired t test was done.

Results

The ABT in the patients studied is shown in Figure 1. It was 6.3 ± 1.09 percent (mean $\pm$ SD) in the control subjects, similar to values in control subjects obtained in our previous studies.[6-8,10-12] In the patients with CAH, the ABT was 3.0 ± 1.8 percent, significantly lower than in the control subjects ($P<0.001$). In the patients with CPH the ABT was 6.0 ± 1.5 percent, similar to that in the controls ($P>0.1$). The ABT in the patients with CAH was not significantly different in patients with CAH having cirrhosis (2.6 ± 1.6 percent) and those without cirrhosis (3.1 ± 2.0 percent) ($P>0.1$) and not significantly different in the HBsAg-positive patients (3.3 ± 2.4 percent) and

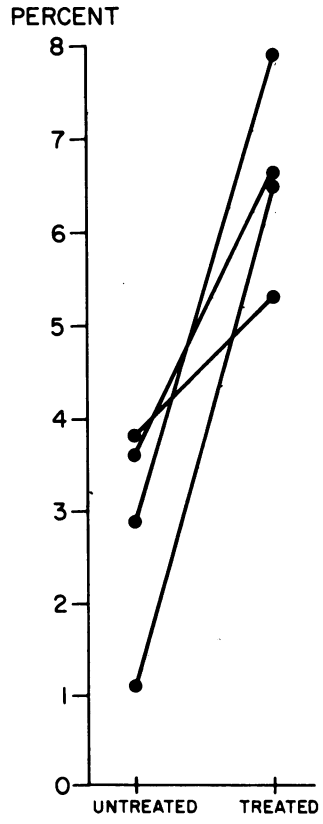

Figure 2.—Results of aminopyrine breath tests in patients with chronic liver disease before and after treatment with prednisone.

the HBsAg-negative patients (3.4±2.1 percent) ($P>0.1$).

In all four patients with CAH studied twice, before and after prednisone therapy, the ABT results returned to normal after therapy (Figure 2). In the six patients with untreated CAH studied twice, at intervals of three to seven days, the ABT results did not change significantly (first ABT 3.5±2.0 percent; second ABT 3.7±2.1 percent, $P>0.1$). The ABT did not change significantly in the four patients with rheumatoid arthritis studied before therapy with prednisone (6.2±1.3 percent) and one month after starting therapy (6.5± 1.6 percent) ($P>0.1$).

Discussion

The ABT findings were normal in our study in all patients with CPH. In contrast, they were abnormal in 20 of 24 patients with CAH. Thus, the data suggest that the ABT may be helpful in evaluating patients with chronic hepatitis. An abnormal ABT result was never found in cases of CPH, and hence in patients with chronic hepatitis it would strongly suggest CAH.

The reason for the abnormal ABT finding in patients with CAH in contrast to that in patients with CPH is unclear. It may have been related to cirrhosis, which is often undetected by needle biopsy in these patients even when it is, in fact, present. It is also possible that there is more hepatic microsomal damage in CAH patients, even without cirrhosis, then in patients with CPH, but such differences have not been observed morphologically. Another possibility is that there is decreased hepatic aminopyrine uptake in these patients, possibly related to portal-systemic shunting.

The improvement of the ABT results in patients with CAH treated with prednisone supports the data from other studies that corticosteroids may be useful in treating this condition. The ultimate verification of this hypothesis will depend on long-term follow-up studies.

In conclusion, the study indicates that in patients with chronic hepatitis and an abnormal ABT finding the diagnosis is extremely likely to be CAH. The potential usefulness of this observation in the workup of patients with chronic hepatitis needs to be evaluated in a prospective study.

REFERENCES

1. Berk PD, Jones EA, Plotz PH, et al: Corticosteroid therapy for chronic active hepatitis. Ann Intern Med 85:523-525, 1976
2. Cook GC, Mullingan R, Sherlock S: Controlled prospective trial of corticosteroid therapy in active chronic hepatitis. Q J Med 40:159-185, 1971
3. Soloway RD, Summerskill WHH, Baggenstoss AH, et al: Clinical, biochemical and histological remission of severe, chronic active liver dsease: A controlled study of treatment and early prognosis. Gastroenterology 63:820-833, 1972
4. Murrary-Lyon IM, Stern RB, Williams R: Controlled trial of prednisone and azathioprine in active chronic hepatitis. Lancet 1:735-737, 1973
5. Wright EC, Seeff LB, Berk PD, et al: Treatment of chronic active hepatitis—An analysis of three controlled trials. Gastroenterology 73:1422-1430, 1977
6. Chadwick RG, Galizzi J, Heathcote EJ, et al: Natural history of chronic persistent hepatitis. Gut 18:951, 1977
7. Hepner GW, Vesell ES: Quantitative assessment of hepatic function by breath analysis after oral administration of [^{14}C] aminopyrine. Ann Intern Med 83:632-639, 1975
8. Hepner GW, Vesell ES, Lipton A, et al: Disposition of aminopyrine, antipyrine, diazepam and indocyanine green in patients with liver disease or on anticonvulsant therapy: Diazepam breath test and correlation in drug elimination. J Lab Clin Med 90:440-456, 1977
9. Hepner GW, Uhlin SR, Harvey HA, et al: Abnormal aminopyrine metabolism in patients with hepatic neoplasm—Detection by breath test. JAMA 236:1587, 1976
10. Bircher J, Kupfer A, Gikalov I, et al: Aminopyrine demethylation measured by breath analysis in cirrhosis. Clin Pharmacol Ther 20:484-492, 1976
11. Galizzi J, Long JG, Billing BH, et al: Assessment of the (^{14}C) aminopyrine breath test in liver disease. Gut 19:40-45, 1978
12. Carlisle R, Galambos JT, Warren WD: The relationship between conventional liver tests, quantitative function tests and histopathology in cirrhosis. Dig Dis Sci 24:358-362, 1979
13. Koretz RL, Lewin KJ, Rebhun DJ, et al: Hepatitis B surface antigen carriers—To biopsy or not to biopsy. Gastroenterology 75:860-863, 1978
14. Winchell HS, Stahelin H, Kusubov N, et al: Kinetics of CO_2-HCO_3 in normal adult males. J Nucl Med 11:711-715, 1970
15. Hepner GW, Vesell ES: Aminopyrine disposition: Studies on breath, saliva and urine of subjects and patients with liver disease. Clin Pharmacol Ther 20:654-660, 1976
16. Hepner GW, Vesell ES: Aminopyrine metabolism in the presence of hyperbilirubinemia due to cholestasis or hepatocellular disease: Combined use of laboratory tests to study disease-induced alterations in drug disposition. Clin Pharmacol Ther 21:213-216, 1977
17. Hepner GW, Vesell ES, Tantum KR: Reduced drug elimination in congestive heart failure: Studies using aminopyrine as a model drug. Am J Med 65:271-276, 1978
18. Hepner GW, Vesell ES: Assessment of aminopyrine metabolism in man after oral administration of ^{14}C-aminopyrine: Effects of phenobarbital, disulfiram and portal cirrhosis. N Engl J Med 291:1384-1388, 1974
19. King C, Toskes P: A caveat: Endogenous CO_2 production increases during non-fasting carbon isotope breath tests. Gastroenterology 74:1049, 1978
20. Soloway RD, Baggenstoss AH, Schoenfield LJ, et al: Observer error and sampling variability testd in evaluation of hepatitis and cirrhosis by liver biopsy. Am J Dig Dis 16:1082-1086, 1971